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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,940	08/20/2001	Felix Kratz	018968-007	4827

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EXAMINER
RUSSEL, JEFFREY E

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 03/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,940	KRATZ, FELIX	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/254,598* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The claim for priority under 35 U.S.C. 120 inserted before the first line of the specification by the preliminary amendment filed August 20, 2001 is objected to because the filing date of the parent application is incorrect. The correct filing date for parent application 09/254,598 is May 21, 1999. Also, the status of the parent application should be updated. Correction is required.

2. Claim 10 is objected to because of the following informalities: At claim 10, page 4 of the amendment filed August 20, 2001, line 7, the comma after "wherein" should be deleted. Appropriate correction is required.

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,310,039. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '039 patent anticipate the instant claims.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

5. Claims 7-9 are rejected under 35 U.S.C. 102(a) as being anticipated by the Beyer et al abstract. The Beyer et al abstract teaches binding a maleimide spacer group to the anticancer drugs chlorambucil, doxorubicin, and daunorubicin and then reacting the derivatized drugs with thiolated transferrin or albumin. An average of 3 to 4 equivalents of the anticancer drug are reacted with each protein molecule.

6. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being obvious over the Beyer et al abstract Application of the Beyer et al abstract is the same as in the above rejection of claims 7-9. The Beyer et al abstract does not teach combining the conjugates with a carrier or an auxiliary agent, and does not teach treating an organism having cancer with the conjugates. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to combine the conjugates of the Beyer et al abstract with carriers or auxiliary agents

because carriers and auxiliary agents are commonly used in the pharmaceutical arts for ease of storage, measurement, and administration of pharmaceutical agents. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the conjugates of the Beyer et al abstract to an organism having cancer because it is prima facie obvious to administer drugs for their intended purpose.

7. Claims 7 and 10-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al. Johnson et al teach reacting diphtheria toxin, which corresponds to Applicant's cytostatic compound, with m-maleimidobenzoyl N-hydroxysuccinimide. The derivatized toxin is then reacted with thiolated transferrin. The conjugates are used to treat cancer, especially erythroleukemia. The toxins are administered in vivo in combination with PBS/0.2% BSA. See, e.g., column 11, line 66 - column 12, line 68; Tables 1-2; and column 15, lines 35-55. Because Johnson et al conjugate the toxin with the transferrin, then at least one molecule of toxin is bound to one molecule of transferrin. Because Johnson et al use a thiolating agent:transferrin molar ratio of 8:1 and because conjugation occurs through thiol groups present in the thiolated transferrin, then at most about 8 molecules of toxin are bound to one molecule of transferrin. Accordingly, Applicant's claimed ratio of about from 1 to 30 molecules of derivatized cytostatic compounds bound to one molecule of transferrin is met. With respect to instant claim 10 and Formula V, while Johnson et al's maleinimide compound has a NHS activating group which is not encompassed by Applicants' definition of Y, the reaction product of Johnson et al's maleinimide compound and the diphtheria toxin will result in the same chemical linkage as will occur in the reaction product between Applicants' maleinimide compound and cytostatic compound, namely an amide bond. Process of making limitations do not impart patentability to

product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. Note also that in instant claim 10, R can be an unsubstituted phenylene group, which corresponds to the phenyl group contributed by the benzoyl in Johnson et al's maleinimide compound.

8. Claims 7-13 are rejected under 35 U.S.C. 103(a) as being obvious over Johnson et al as applied against claims 7 and 10-13 above, and further in view of the Nathan et al article. Johnson et al disclose the use of diphtheria toxins as cytostatic compounds, and do not teach the use of doxorubicin as a cytostatic compound. The Nathan et al article teaches that doxorubicin is one of the most widely used anthracycline antibiotics, that doxorubicin has a broad spectrum of activity against solid tumors, and that doxorubicin comprises an amino group available for conjugation through formation of an amide bond. See page 240. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to substitute the doxorubicin of the Nathan et al article for the diphtheria toxins in the conjugates of Johnson et al because doxorubicin's amino group would be available for conjugation by the same reaction mechanism used by Johnson et al and because the use of doxorubicin instead of diphtheria toxins would permit treatment of a broader spectrum of cancers.

9. Claims 7-13 are rejected under 35 U.S.C. 103(a) as being obvious over Johnson et al in view of the Nathan et al article as applied against claims 7-13 above, and further in view of the Beyer et al abstract or Willner et al. As noted above, Johnson et al do not teach the use of doxorubicin as a cytostatic compound, but Johnson et al in combination with the Nathan et al article are deemed to suggest the substitution of doxorubicin for diphtheria toxins in the conjugates of Johnson et al. This substitution would further have been obvious to one of

ordinary skill in the art at the time Applicants' invention was made in view of the Beyer et al abstract and Willner et al (see, e.g., column 3, line 59, and column 4, line 5 - column 5, line 13), which show that in the conjugate arts it is routine to substitute one known drug for another while maintaining the same spacers and carriers/targeting agents.

10. Claims 7-13 are rejected under 35 U.S.C. 103(a) as being obvious over Johnson et al in view of the Nathan et al article as applied against claims 7-13 above, and further in view of Jansen et al. Johnson et al's maleimido compound comprises a phenylene spacing structure rather than an aliphatic carbon chain as required by Applicants' formula V. Like Johnson et al, Jansen et al also disclose conjugating a cytostatic compound comprising an amino group with a thiolated targeting agent by first derivatizing the cytostatic compound with a spacer compound having a maleimido group. In Jansen et al's spacer compound, the spacing structure R_8 can be either aliphatic or aromatic containing from 1 to 15 carbon atoms. Specifically exemplified is a spacing structure E, equivalent to R_8, which is $(CH_2)_5$. See, e.g., column 12, line 44 - column 13, line 43; Examples 2, 8, and 10; and claim 10. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to substitute the aliphatic spacing structures of Jansen et al for the phenylene spacing structure of Johnson et al in the conjugates of Johnson et al as modified above by the Nathan et al article because Jansen et al disclose aliphatic and aromatic spacing structure to be equivalent spacing structures and the substitution of one functional equivalent for another is prima facie obvious, and because the use of a variable length aliphatic spacing structure would permit optimization of the spacing distance and hence optimization of the activity of the conjugates.

11. Claims 7-13 are rejected under 35 U.S.C. 103(a) as being obvious over Hannart et al in view of Imakawa. Hannart et al teach conjugates of vinca alkaloids such as vinblastine, vindesine, or vincristine, through a spacer molecule having a spacing structure X which can be a linear alkylene chain of 1 to 12 carbons and having a maleinimide group, to a protein which can be bovine or human serum albumin and to which can be added free thiol groups for conjugation. Exemplified are spacing structures having six carbon atoms. See, e.g., column 2, lines 37-57; column 3, lines 11-62; column 4, lines 33-35; column 5, line 16 - column 6, line 12; and Examples 3, 10, and 18. Hannart et al do not specifically teach the use of a thiolated albumin. Imakawa teaches that albumin can be thiolated for use in forming conjugates. See column 23, line 66 - column 24, line 11. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form the conjugates of Hannart et al using thiolated albumin as the protein because bovine and human serum albumin are specifically exemplified by Hannart et al as preferred proteins to be conjugated and because Imakawa teaches that albumin can be thiolated for the purposes of conjugation.

12. Claims 7 and 11-13 are rejected under 35 U.S.C. 103(a) as being obvious over the Motsenbocker et al article. The Motsenbocker et al article teaches methylene blue, which corresponds to Applicant's cytostatic compound, conjugated through a spacer molecule having a succinimido group, to BSA, which is then conjugated to a Fab antibody fragment through a N,N'-bis(3-maleimidopropionyl)-2-hydroxy-1,3-propane-diamine group. See, e.g., page 649, column 2, last two paragraphs and Figure 2, and page 650, column 1, first paragraph. Concerning Applicant's claim limitation "thiolated albumin", note that the claims do not specify how thiolation is to occur, and that the Motsenbocker et al article's denaturing step results in the

formation of free thiol groups, i.e. is a thiolation process. The Motsenbocker et al article does not teach using methylene blue conjugated through a spacer molecule having a maleimido group in these conjugates, and does not teach Applicant's claimed ratio of cytostatic compounds to albumin. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use a maleimido group instead of a succinimido group in forming the above conjugates of the Motsenbocker et al article because the Motsenbocker et al article discloses how to derivatize methylene blue with a maleimido group, because thiol groups are disclosed by the Motsenbocker et al article to be present in denatured BSA for reaction with a maleimido group, and because substitution of one known functional group for another is prima facie obvious in the conjugation art. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal ratios of methylene blue to albumin in the conjugates of the Motsenbocker et al article because reactant ratio and drug:carrier ratio are art-recognized result-effective variables which are routinely determined and optimized in the conjugate art.

13. Claim 14 is rejected under 35 U.S.C. 103(a) as being obvious over the Motsenbocker et al article as applied against claims 7 and 11-13 above, and further in view of Hannart et al. The Motsenbocker et al article teaches targeting methylene dyes using anti-tumor antibodies (see, e.g., page 648, column 1, third full paragraph), but does not teach antibodies specific to the tumors recited in instant claim 15. Hannart et al teach the use of antibodies specific to, e.g., melanoma, breast, and lung cancer cells for use in forming conjugates for anti-cancer therapy (see, e.g., column 4, line 50 - column 5, line 15). It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form the conjugates of the

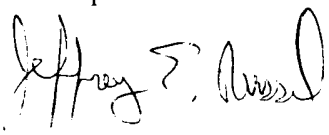
Motsenbocker et al article using the antibodies of Hannart et al because the conjugates of the Motsenbocker et al require anti-tumor antibodies, because the antibodies of Hannart et al would permit the conjugates of Motsenbocker et al to be applied against a wide variety of cancers, and because substitution of a known species for a known genus is prima facie obvious.

14. Claims 7-10, 12, and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by the Kratz et al article. The Kratz et al article teaches binding a maleimide spacer group to the anticancer drug daunorubicin and then reacting the derivatized drug with thiolated transferrin. An average of 3.1 equivalents of the anticancer drug are reacted with each protein molecule. The conjugate is combined with physiological buffer. See, e.g., Scheme I and page 621, second full paragraph.

15. The examiner maintains his position for the reasons set forth during prosecution of the parent application.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel
Primary Patent Examiner
Art Unit 1654

JRussel
March 5, 2003